REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 37-39, 42-49, 52-57 and 59-65 stand rejected under 35 U.S.C. §112, first ¶, as lacking enablement.

The Examiner states that: (i) the Fletcher Declaration is not persuasive because the results of the Myloral trial do not rule out the possibility that the effects of the drug on autoimmune disease are due to placebo alone, (i.e., that clinical results for placebo were better than for the drug, and therefore the drug is ineffective); (ii) the EAE and NOD mouse models are not reasonably predictive of human response to bystander antigens; and (iii) it is doubtful that administration of a bystander antigen after onset of diabetes will have any effect on disease.

Applicants respectfully disagree with the Examiner's conclusions for the reasons outlined below.

It is respectfully submitted that the results of the Myloral Phase III trials do not show that myelin administration is ineffective, and that the conclusions discussed in detail in the Fletcher Declaration should be accepted absent a compelling reason to the contrary.

It is submitted that the results from this and prior trials are encouraging and indicate merely that further trials should be performed (Fletcher Declaration, ¶¶ 9,11). For example, Exhibit I (attached to the Fletcher Declaration) shows the annual attack rate before and after treatment in the U.S. Phase III clinical trials of four multiple sclerosis drugs. Three of these drugs (Betaseron, Avonex, and Copaxone) have already been approved for commercial sale in the U.S. for treating multiple sclerosis. The results depicted in the graph establish that the annual

attack rate for multiple sclerosis patients who received Myloral in the AutoImmune Phase III clinical trial decreased substantially in comparison to the control (Fletcher Declaration, ¶ 6). Furthermore, use of the Myloral composition resulted in approximately the *same* reduction in attack rate as for each of the three approved drugs. However, beneficial effects of Myloral are believed to have been masked by a strong placebo effect, which is believed to have resulted from the fact that Myloral has no side effects and therefore patients could not determine if they were receiving a placebo or an active agent (Fletcher Declaration, ¶ 7). Beneficial effects of Myloral were also seen when Myloral was administered in combination with beta-interferon (Fletcher Declaration, ¶ 8). Additional encouraging magnetic resonance imaging results measuring lesion load were obtained with respect to a particular genetic subgroup of patients treated with Myloral (Fletcher Declaration, ¶ 10). Based on this, Dr. Fletcher properly concludes that the Phase III Myloral results do not indicate lack of efficacy, but are encouraging (Fletcher Declaration, ¶ 12).

The Examiner states that results regarding a combination of Myloral and beta-interferon cannot be properly relied upon because the claims are not limited to that combination.

However, it is not necessary to applicants to limit the claims to administration to the subset of patients who will benefit. It is submitted that if administration to the population in general results in a benefit to those taking beta-interferon, then the invention has appropriate usefulness under 35 U.S.C. §112.

It is also noted that beta-interferon is commonly administered to MS patients, and that those taking beta-interferon represent a substantial proportion of MS patients.

It is submitted that any of these beneficial effects alone is sufficient to meet applicable §112 requirements.

Applicants respectfully point out that the Declaration of Dr. George Eisenbarth indicates that the NOD model is (in fact) a standard diabetic model. In particular, the declaration states that the NOD mouse model is a recognized animal model frequently used to study autoimmune diabetes. Dr. Eisenbarth states that the NOD mouse model is "the best model of Type 1 diabetes available" (Eisenbarth Declaration ¶ 10). The model has been used to test effectiveness of many drugs including cyclosporin A, now a recognized nonspecific immunosuppressant (Eisenbarth Declaration, ¶ 10).

The Examiner notes that the copy of the Eisenbarth Declaration submitted was not accompanied by certain referenced exhibits. Applicants only rely on paragraphs 8-12 of the Declaration (relating to the NOD mouse model). Copies of Dr. Eisenbarth's *curriculum vitae* and the Eisenbarth and Jackson reference are enclosed. The Foulis reference was not enclosed with the original of the Declaration, but can be provided should the Examiner indicate that it would be helpful. The Weiner declaration referenced in paragraph 11 is not presently relied on.

It is respectfully submitted that Dr. Eisenbarth's declaration is substantial evidence in itself that supports withdrawal of the outstanding rejection.

However, the Examiner is also referred to the enclosed Daniel reference, which exemplifies the conventional reliance in this art on the NOD mouse model as providing results

predictive of usefulness in type I diabetes treatment or prevention. Similarly, Maron et al., also cited below, rely on the same model.

The Examiner states that administration of a bystander antigen after onset of the disease will not have any effect, citing statements in the Eisenbarth declaration concerning administration of insulin to patients suffering from overt diabetes, and in particular those having suffered from overt diabetes for more than one year.

Applicants respectfully point out that early onset type I diabetics can be treated with immunosuppressive agents (while, as noted by the Examiner and Dr. Eisenbarth, later stage diabetics have totally lost beta cell function and cannot be treated).

For example, enclosed with this amendment is an article by Bach that indicates that immunosuppressive agents can be used to treat overt type I diabetes, (and to prevent diabetes, or induce remission of diabetes) (*see*, Tab 1:Bach, Strategies in Immunotherapy of Insulin-Dependent Diabetes Mellitus, In, Immunosuppressive and Antiinflammatory Drugs, New York Academy of Sciences, pg. 365, Table 1 and pg. 366, Table 2 (1993)).

It is noted that when type I diabetes is first diagnosed, substantial beta cell function normally remains (although much has been destroyed). The purpose of treatment with the invention is to prevent further, complete destruction of beta cells (as in the treatment described by Bach).

It is also noted that the assignee of the present application is currently conducting clinical trials concerning suppression of autoimmune response in type I diabetes by oral

administration of insulin to early onset diabetics (those who are termed "newly diagnosed"). This treatment is, as with the present invention, aimed at preventing destruction of the functional beta cells remaining at the time type I diabetes is normally first diagnosed.

A copy of a reference of Coutant et al. presented as a poster at the June 1998 American Diabetes Session is enclosed, describing preliminary results in those trials. Although data for only a small number of subjects have been analyzed thus far, the data are said to be "promising" for adult patients.

The method is discussed in the reference in the context of "antigen driven bystander suppression".

Thus, it is submitted that those skilled in this art believe that type I diabetes can be immunologically treated at the early onset stage.

The Examiner doubts that insulitis and diabetes are sufficiently related for results in the specification to support the claimed method.

Applicants respectfully point out that insulitis in NOD mice has the immunological and pathological features of type I diabetes. Specifically, type I diabetes is a T cell mediated disease and insulin-specific T cells (in particular TH1 cells) are the predominant component of the islet infiltrates that accumulate in NOD mice (*see* Tab 2: Daniel et al., Intranasal Administration of Insulin Peptide B: 9-23 Protects NOD Mice from Diabetes, at page 371 first paragraph, In, Oral Tolerance Mechanisms and Applications, Annals New York Academy of Sciences 778: 371 (1996); *see also* Tab 3: Maron et al. Oral Tolerance to Insulin and the Insulin B-chain, at page

346, first paragraph, In, Oral Tolerance Mechanisms and Applications, Annals New York Academy of Sciences 778: 346 (1996)).

Furthermore, human administration of insulin has, as reported in the Coutant reference, provided encouraging results, supporting a link between results obtained in the NOD mouse model, in which insulitis occurs, and those in type II diabetic patients.

The Examiner notes that GAD is an autoantigen. Results at Example 5 of the present specification, however, describe administration of glucagon in the NOD model. Glucagon is solely a bystander antigen.

The Examiner questions whether ongoing autoimmune response can be treated.

With respect to this issue, namely, whether the suppression of autoimmunity can be induced after onset of the autoimmune response, applicants enclose a copy of WO 88/10120, which demonstrates treatment of an ongoing immune response in EAE at Table 2 (oral administration 2, 5 or 7 days after immunization) and Table 3 (oral administration 7 days after immunization). This disclosure provides substantial (unrebutted) evidence that treatment after onset of autoimmunity is also effective.

In view of the above remarks, applicants respectfully request that the Examiner withdraw the rejection of claims 37-39, 42-49, 52-57 and 59-65 under 35 U.S.C. §112, first paragraph for lack of enablement.

REJECTION UNDER 35 U.S.C. §102

Claims 48-49, 52-55 and 56, 62, 63 and 64 stand rejected under 35 U.S.C. §102(b) as anticipated by pages 1087-1088 of the Merck Manual.

Applicants have amended independent claims 48 and 57 to recite that the dosage form is contained in an inhaler or nebulizer. The Merck Manual contains no teaching or suggestion of such a form.

Withdrawal of the rejection of claims 48-49, 52-55 and 56, 62, 63 and 64 under 35 U.S.C. §102(b) as anticipated by the Merck Manual is respectfully requested.

DOUBLE PATENTING REJECTIONS

Applicants intend to file an appropriate terminal disclaimer over the applications that provisional double-patenting rejections are based on once there is an indication of allowability.

NEW REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 37-39, 42-49, 52-57, and 59-65 stand rejected under 35 U.S.C. §112, first paragraph on the basis that those claims contain new matter.

The Examiner states that support is lacking in the specification for "nasal".

At page 23, line 30 the present specification states:

> The inhalation mode of administration is preferably not through the nasal passages but through the bronchial and pulmonary mucosa.

It is respectfully submitted that this passage conveys to one skilled in the art that "nasal" administration is necessarily encompassed by the invention. If it were not encompassed, bronchial and pulmonary mucosal administration could not be said, as stated in the specification, to be "preferred".

In other words, this statement necessarily teaches that "nasal" administration is the "non-preferred" mode of administration by inhalation, i.e., that it is encompassed by the invention, but is not the preferred route of administration.

The Examiner also states that "adapted for nasal or oral administration" is not supported by the specification. This language has been deleted.

Withdrawal of the rejection of claims 37-39, 42-49, 52-57, and 59-65 under 35 U.S.C. §112, first paragraph on the basis that those claims contain new matter is respectfully requested.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 60, 61, 63, and 64 stand rejected on the basis that the term "substantially" is indefinite.

It is respectfully submitted that the phrase "substantially pure" or "substantially free" is commonly accepted in this art, as well as in this particular examining group, as being a definite way to claim a composition of matter.

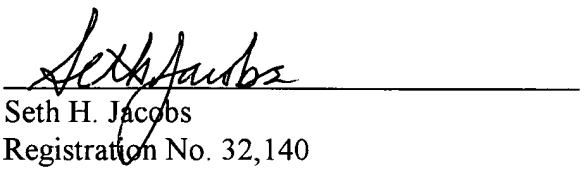
Withdrawal of this rejection is respectfully requested.

CONCLUSION

It is submitted that the pending claims are now in condition for allowance.

Issuance of a Notice to that effect is earnestly solicited.

Respectfully submitted,



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